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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/068,299	02/06/2002	Fiona M. Wood	AVT-001	8540

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

MAIL DATE	DELIVERY MODE
12/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/068,299	WOOD ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,34-63,65 and 67-79* is/are pending in the application.

4a) Of the above claim(s) *34-60,62 and 67-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,61,63,65 and 75-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/09 has been entered.

Response to Amendments

Applicant's amendments filed 10/19/09 to claims 29, 61, and 65 have been entered. Claims 64 and 66 have been canceled. Claims 75-79 have been added. Claims 29, 34-63, 65, and 67-79 remain pending in the current application, of which claims 29, 61, 63, 65, and 75-79 are being considered on their merits. Claims 34-60, 62, and 67-74 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

The amendment to claim 61 is not fully compliant with 37 C.F.R. 1.121(c). Specifically, the matter in brackets in step (b) should be struck-through, not placed in brackets; five or fewer consecutive characters may be deleted by enclosing them in double brackets. However, in the interest of compact prosecution, and considering applicant's description of the amendments at page 9 of the remarks, the examiner

agrees to consider the claims on their merits, interpreting the phrase "the cells being provided in" as being deleted from step (b) of claim 61. **Future submissions that do not comply fully with 37 C.F.R. 1.121 will be considered nonresponsive.**

Claim Objections

Claim 65 is objected to because of the following informalities: It should read, "wherein said composition of cells comprise**s** keratinocyte …" to comply with standard English. Appropriate correction is required.

Claim 76 is objected to because of the following informalities: It should read, "trypsin-EDTA," i.e. "EDTA" in all capital letters. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29, 61, 63, 65, and 75-79 are/remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "dermal-epithelial" in claims 29 and 61 is queried. Dermal tissue inherently contains epithelium, and the specification refers to the "dermal-epithelial junction" (page 11, lines 12-20). It is not clear whether the claim term refers simply to any dermal sample such as the biopsy obtained in the working example at page 21, lines 8-14, or whether it is necessarily limited to the cells at the dermal-epithelial junction (such as those obtained at page 22, lines 10-14, of the specification). Clarification is required.

Claims 29 and 61 also recite a cell composition "having a ratio of keratinocyte basal cells, fibroblasts, and melanocytes that is comparable to a ratio of keratinocyte basal cells, fibroblasts, and melanocytes present in [a patient or a tissue sample from which the population is obtained]," which is confusing. First, a ratio is, by definition, a comparison of two numbers, so the meaning of a ratio of three values is not clear. Second, in reciting "a ratio" (as opposed to "the ratio"), the term does not limit the claimed ratio to any particular one, e.g. the ratio of the total number of one cell type to the total number of another cell type within the population. Third, the criteria for determining whether one ratio is "comparable" to another are not clear; all numbers are literally comparable to each other in that it is possible to compare them. Clarification is required.

Claim 61 requires "a composition of cells derived from said tissue sample," but the word "derived" does not clearly set forth the relationship between the cells and the sample. It is not clear to what degree, if any, the tissue may be manipulated and still yield cells "derived" from it. The claim does not, for example, require that the composition contain both dermal and epithelial cells, since epithelial cells are "derived" from a tissue sample containing both dermis and epidermis. Clarification is required.

Because claims 63, 65, and 75-79 depend from indefinite claim 61 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claims 78 and 79 require that the trypsin in the composition be "present in a solution in an amount that is between 5 and 0.1% per volume of the solution," but it is

not clear whether this limitation addresses the concentration of trypsin in the solution that is added to the suspension to yield the composition or whether it addresses the final concentration of trypsin in the claimed composition. The as-filed specification implies that the former is the case (page 21, lines 20-25); nowhere does the specification address the final concentration of trypsin in the finished cell composition. The claim should clearly limit the components of the claimed product.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 29, 61, 63, 65, and 75-79 are rejected under 35 U.S.C. 102(b) as being anticipated by Noel-Hudson et al. (1993, *In Vitro Cell and Developmental Biology – Animal* 31: 508-515; reference C6 on 6/1/04 IDS) taken in light of Van Bossuyt (1999, U.S. Patent 5,866,167; reference A). The claims are interpreted as being drawn to a composition comprising cells, said cells having been dissociated from some tissue, and a nutrient solution, said composition lacking large aggregates of cells. In some dependent claims, the cells are obtained during the course of a surgical operation. In some dependent claims, the composition further comprises an enzyme, e.g. trypsin.

Noel-Hudson et al. teach a composition comprising cells dissociated from human foreskin tissue biopsy fragments with 0.25% trypsin and then with a solution comprising 0.025% trypsin (page 509, column 1, paragraph 7). Noel-Hudson's composition lacks

all cell aggregates of any size ("individual cells;" *ibid.*) and comprises a physiological saline, specifically Hanks' solution with calcium salts (*ibid.*).

Van Bossuyt is cited solely as evidence that skin (such as the skin biopsy fragments of Noel-Hudson) inherently contains keratinocytes (epithelial cells), melanocytes, and Langerhans cells in the epidermis; proliferating keratinocytes at the base of the epidermis; and fibroblasts in the dermis (column 1, lines 41-53).

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' cell suspension differs, and if so to what extent, from the suspension discussed in Noel-Hudson. The prior art suspension is made by dissociating skin samples with trypsin, as is the instant composition (Example 1 at page 21, et seq.); furthermore, Van Bossuyt's teachings indicate that the whole-skin biopsy of Noel-Hudson inherently contains all of the cell types recited in claims 29, 61, and 65. The cited art taken as a whole demonstrates a reasonable probability that the suspension of the prior art is either identical or sufficiently similar to the claimed suspension that whatever differences exist are not patentably significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants.

The fact that Noel-Hudson does not specifically discuss the presence of the cell types recited in claims 29, 61, and 65 in their suspension does not make that suspension patentable. Applicant's suspension possesses inherent characteristics which might not be displayed in the tests used in Noel-Hudson; it is noted that all of the cell types recited in claims 29, 61, and 65 are inherently present in skin tissue. Clear

evidence that the suspension of the cited prior art does not possess a critical characteristic that is possessed by the claimed suspension (e.g., the presence of all of the recited cell types) would advance prosecution and might permit allowance of claims to applicants' suspension.

Claim 29 is a product-by-process claim. M.P.E.P. § 2113 reads, "Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps." **Once a product appearing to be substantially identical is found and an art rejection made, the burden shifts to the applicant to show an unobvious difference**. In this case, this rejection might be overcome by a substantive evidentiary showing that the method steps recited in the cited claims produce a composition that is materially and patentably distinct from the skin cell suspension of Noel-Hudson.

Applicants state that Noel-Hudson does not teach all of the limitations of the claimed compositions because Noel-Hudson's composition allegedly contains calf serum. These arguments have been fully considered, but they are not persuasive. Applicant has mischaracterized the teachings of Noel-Hudson. The paragraph relied upon by the examiner reads:

> *Cells and culture conditions.* Human keratinocytes were isolated from human foreskin of [a] 1-yr-old donor, as described by Boyce and Ham (7). Briefly, the biopsy fragments were first treated with 0.25% trypsin (wt/vol) and 1000 U/ml collagenase (wt/vol) in Hanks' solution containing Ca++ for 2 h at 37° C, then with a 0.025% trypsin (wt/vol): 0.01% EDTA (wt/vol) solution to release individual cells.

The procedure discussed in this paragraph yields a suspension of foreskin tissue (and, therefore, all cell types inherently present therein) in a calcium solution containing trypsin and lacking any serum whatsoever. The fact that Noel-Hudson subjected their suspension to further culturing steps is irrelevant here. The suspension yielded by the method in this paragraph anticipates or renders obvious the claimed suspension.

Claims 29, 61, 63, and 75-79 are rejected under 35 U.S.C. 102(b) as being anticipated by Hirobe (1991, *Journal of Experimental Zoology* 257: 184-194; reference U). The claims are interpreted as being drawn to a composition comprising cells, said cells having been dissociated from some tissue, and a nutrient solution, said composition lacking large aggregates of cells. In some dependent claims, the cells are obtained during the course of a surgical operation. In some dependent claims, the composition comprises an enzyme, e.g. trypsin.

Hirobe teaches a composition comprising cells dissociated from mouse whole skin tissue by cutting the tissue into small pieces and incubating the pieces tissue in a 0.25% solution of trypsin (page 185, under “Culture of melanocytes”). The composition of Hirobe is a suspension of single cells (*Id.*). and comprises a serum-free physiological saline, specifically melanoblast defined medium, which comprises salts (*Id.*).

Claim 29 is a product-by-process claim. Once a product appearing to be substantially identical is found and an art rejection made, the burden shifts to the applicant to show an unobvious difference. In this case, this rejection might be overcome by a substantive evidentiary showing that the method steps recited in the

cited claims produce a composition that is materially and patentably distinct from the skin cell suspension of Hirobe. See M.P.E.P. § 2113. The discussion of inherent properties in the rejection over Noel-Hudson also applies to this rejection for similar reasons.

Regarding the previous art rejection over Hirobe (1992, *Journal of Cellular Physiology* 162: 337-345), applicant alleges that the composition does not contain the ratios of cells instantly claimed or a composition lacking serum. See reply, page 12, last paragraph. These arguments have been fully considered, but they are not persuasive.

As discussed in the indefiniteness rejections above, the limitations regarding the "comparable" "ratios" do not particularly point out and distinctly describe the invention. The composition of Hirobe is produced from a sample that has been enzymatically dissociated; therefore, the composition contains those cells that were present in the tissue sample. There is no disclosure in Hirobe that any cells have been destroyed, so the amount of each type of cell relative to each other is comparable to that in the tissue; "comparable" is not synonymous with "identical."

Regarding the presence of serum, Hirobe clearly teaches that the cells released by the enzymatic digestion step and dissociated with the Pasteur pipette are resuspended in MGM, a serum-free medium; serum is only added when the cells are placed into a dish. The fact that Hirobe later adds serum to a serum-free composition does not negate Hirobe's teaching of that serum-free composition.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651